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Positron emission tomography-computed tomography for staging and follow-up of pediatric nasopharyngeal carcinoma

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Abstract

Purpose—While evaluations of FDG PET-CT in adult patients with NPC have documented advantages and disadvantages of the technique compared with conventional imaging, to our knowledge, no such studies have been performed with pediatric patients. In this investigation, we studied the utility of FDG PET-CT in children with NPC.

Methods—Eighteen children with biopsy-proven NPC who underwent FDG PET-CT and MRI were studied (total 38 pairs of imagings). All baseline and follow-up FDG PET-CT and MRI studies were independently reviewed for restaging of disease.

Results—The concordance between FDG PET-CT and MRI in T, N, and overall staging was 29%, 64%, and 43%, respectively. Compared with MRI, FDG PET-CT yielded lower T and overall staging and showed less cervical and retropharyngeal lymphadenopathy. The concordance between follow-up FDG PET-CT and MRI was 79% overall and 100% 9 months after therapy. In patients who achieved complete remission, FDG PET-CT showed disease clearance 3-6 months earlier than MRI. There were no false positive or false negative FDG PET-CT scans during follow-up.

Conclusions—FDG PET-CT may underestimate tumor extent and regional lymphadenopathy compared with MRI at the time of diagnosis, but it helps to detect metastasis and clarify ambiguous findings. FDG PET-CT is sensitive and specific for follow-up and enables earlier determination of disease remission. FDG PET-CT is a valuable imaging modality for the evaluation of and monitoring NPC in pediatric patients.

Keywords

positron emission tomography; magnetic resonance imaging; nasopharyngeal carcinoma; child

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

INTRODUCTION

NPC is uncommon in children, with an incidence of only 0.1-1.5/1,000,000/year in the US [1]. NPC is classified pathologically into 3 subtypes: type I, or keratinizing squamous cell carcinoma, the most common form in the United States, often associated with alcohol and tobacco use; type II, or non-keratinizing squamous cell carcinoma; and type III, or undifferentiated carcinoma [2]. Unlike in adults, type III is the most common subtype in children, while type I is the least common [3]. Children with NPC usually present with painless cervical lymphadenopathy [3]. The median age at diagnosis is 13 years. NPC may extend into the skull base and cause cranial nerve VI and XII dysfunction, resulting in diplopia or dysphonia. The differential diagnosis includes primary and secondary tumors that may involve the nasopharynx, such as rhabdomyosarcoma and non Hodgkin lymphoma. Treatment includes chemotherapy and radiotherapy. The outcome for children is usually better than for adults.

Current methods to evaluate the disease at diagnosis and follow-up include CT, MRI, and bone scan. MRI is the preferred imaging modality for determining loco-regional disease extent because of its excellent delineation of anatomic detail [4]. Investigators have recently utilized FDG PET alone or combined with CT (FDG PET-CT) to evaluate NPC patients. Advantages of FDG PET are that it can provide semiquantitative information about the functional activity of the tumor, detect areas of involvement that may be overlooked by MRI, distinguish active tumor from scar tissue, and evaluate the whole body in a single imaging session. Some studies found that FDG PET or FDG PET-CT can contribute to staging [5-8] and has high sensitivity and specificity in diagnosing residual and recurrent disease [9-11]. There are also studies, however, showing that FDG PET or FDG PET-CT may not provide additional information beyond MRI and have low spatial resolution and high false positives [12, 13]. The value of FDG PET-CT compared with conventional imaging in NPC patients, therefore, remains inconclusive. These studies were composed largely of adults with only a few adolescents. Whether these data are applicable to children is uncertain, especially in view of the differences between children and adults in NPC biology. We performed the current study to evaluate the utility of FDG PET-CT compared with MRI for staging and follow-up evaluation in pediatric NPC patients.

METHODS

With institutional review board approval, we reviewed the medical records and imaging studies of all patients below 18 years with biopsy-proven NPC who underwent FDG PET-CT and treatment treated at St. Jude Children's Research Hospital from January 2003-June 2009. We report the demographics, histopathology, imaging findings, treatments, and outcomes.

Treatment of patients

Patients were treated with three cycles of induction chemotherapy with cisplatin and 5-fluorouracil followed by concurrent radiotherapy and chemotherapy with cisplatin or chemoradiotherapy up front followed by adjuvant chemotherapy. Radiation therapy was delivered with a conformal or intensity modulated technique to cumulative doses of 6120-6600cGy. Amifostine was used for salivary gland protection and renal protection as tolerated by patients.

Imaging protocol and review

For FDG PET-CT examinations, 5.5MBq/kg [¹⁸F]-FDG (maximum 444MBq) was injected intravenously following an overnight fast, or minimum 4 hour fast for afternoon studies.

Blood glucose was determined prior to injection of [18 F]-FDG and was normal. Patients were kept in a quiet dark room after injection and encouraged to remain recumbent with arms resting at the sides and relaxed. Transmission CT images for attenuation correction and lesion localization, and PET emission images were acquired approximately 1 hour later using a GE Discovery LS PET/CT system (GE Medical Systems, Waukesha, WI) with patients' arms at their sides. CT acquisition parameters were slice thickness of 0.5cm, 0.8-s tube rotation, table speed 1.5cm/rotation, pitch 1.5:1, 120kV, 90mA, with dose modulation. PET images were obtained from the top of the skull through the feet for 5min per bed position in 2D mode with arms at patients' side. Images were reconstructed using standard vendor supplied software. FDG PET-CT scans for each patient were reviewed by 2 nuclear medicine physicians without knowledge of clinical information. SUV_{max} was determined from manually regions of interest (ROI) placed over the tumor activity in multiple planes. The size of the ROI depended on the size of the tumor activity. There was not a minimum size. The background was that of surrounding non-involved tissue. Uptake was considered abnormal if it was increased above that of surrounding background and could not be explained by accumulation in a normal structure. Since all the studies were performed on PET-CT units, brown adipose tissue could be identified on CT as areas of low attenuation in typical locations.

MRI examinations of the neck were obtained using head and neck matrix coils to image the area from approximately the superior level of the temporal lobes to the sternal notch. The examinations consisted of unenhanced spin-echo sagittal T1-weighted, spin echo axial T1-weighted, spin echo coronal T1-weighted, fast spin echo axial proton density, fast spin echo axial T2-weighted, and coronal STIR pulse sequences.

Post-gadolinium axial and coronal T1-weighted pulse sequences were also obtained using the parameters outlined above following the intravenous administration of Gd-DTPA gadodiamide (Omniscan, GE Healthcare, Princeton, NJ) or gadopentate dimeglumine (Magnevist, Bayer Healthcare, Wayne, NJ). Fat saturation was used for the post-gadolinium images for one of the studies conducted at our institution and subtraction of T1-weighted images before and after contrast was performed for all the other examinations obtained at our facility. Twenty-five examinations were performed on a 1.5-T MRI system (either a Siemens Symphony or Avanto unit). Twelve studies were completed on a 3-T MRI system (Siemens Trio). One study was referred from an outside institution and was performed on a 1.5-T Philips Intera Achieva MRI unit. Fat saturation was used for the post-contrast images submitted with this outside examination.

One experienced pediatric neuroradiologist reviewed the MRI studies without knowledge of clinical information. The size of the tumor was reported as the maximum anteroposterior or transverse diameter in the axial plane. Jugulodigastric and retropharyngeal LNs were considered metastatic if their short-axis diameter in the axial plane was greater than or equal to 1.1cm or 6mm respectively [14]. LNs measuring greater than or equal to 1.0cm in all other areas were considered metastatic. These size criteria for cervical lymph nodes reflect those widely used in the literature [12-21]. Any LN with necrosis and groups of 3 or more borderline-sized LNs also qualified as metastatic [13, 15]. The presence of extranodal metastases was also assessed with bone scan and chest CT, which form part of the conventional imaging modality.

In this study, patients with baseline scans were restaged by conventional imaging (MRI, chest CT and bone scan) or FDG PET-CT independently according to the most recent version of the AJCC NPC staging classification [22]. For follow-up imaging, a false positive result was defined as residual abnormality that was not shown concurrently on the other imaging modality, subsequently disappeared or remained stable, or was determined by

biopsy not to be malignant. A false negative result was defined as the absence of a lesion on one imaging modality that was seen concurrently on the other imaging modality and that subsequently progressed or was confirmed by biopsy to be malignant.

EBV-VCA (Epstein Barr virus viral capsid antigen) Ig levels were recorded for correlation with tumor uptake of FDG.

Statistical analysis

The agreement between FDG PET-CT and conventional staging was measured by Cohen's kappa [23]. The maximum value of 1 indicates the measurements are in complete agreement. Landis interprets kappa as follows: <0- no agreement, 0 to 0.2—slight agreement, 0.2 to 0.4—fair agreement, 0.4 to 0.6—moderate agreement, 0.6 to 0.8—substantial agreement, 0.8 to 1.0—almost perfect agreement[24]. Because of small sample size, AJCC substages were dropped for some analyses. Wilcoxon signed-rank test was used to test the difference between FDG PET-CT and MRI measurements. Jonckheere-Terpstra test was used to analyze the association between SUV_{max} and staging. Spearman's rank correlation was used to test the association between SUV_{max} and size of the tumor. Binomial test was used to compare LNs found by FDG PET-CT and MRI.

RESULTS

Eighteen patients had FDG PET-CT and MRI performed in January 2003-June 2009 (total 38 pairs of imagings). All patients also had chest CT and 17 patients had bone scan at diagnosis. Their characteristics are shown in Table 1. All patients had cervical lymphadenopathy at presentation. None had distant metastasis according to chest CT and bone scan. One patient had metastatic relapse in the lungs and mediastinum at 9 months after initial diagnosis and died at 2.6 years after diagnosis. The remaining patients were alive in continuous remission with a median follow-up of 4.5 years (range, 2.0-9.7 years).

Fourteen patients (78%) had both FDG PET-CT and MRI at baseline. Six of these 14 patients also had follow-up FDG PET-CT, with 5 patients having paired MRI for comparisons. Four patients only had follow-up FDG PET-CT without baseline FDG PET-CT because they were initially diagnosed in another institution before referral to us, and 3 of them had paired MRI for comparisons. All patients with baseline studies were alive without disease at the last follow-up.

FDG PET-CT at diagnosis

For the 14 patients with both FDG PET-CT and MRI at baseline, the scans were performed a median of 2.5 days apart (range, 0-12 days apart). In three patients FDG PET-CT scans were obtained 4-6 days after initiation of chemotherapy. No substantial head motion was noted, indicating good alignment of the PET and CT images

Table 2 shows the size of the primary tumor, staging, and SUV_{max} . The overall staging was the same by PET-CT and MRI in only 43% of the patients. The agreement was slight and statistically insignificant (kappa=0.104 Table 3a). The agreements on T and N stagings were 29% (kappa=0.0870, Table 3b) and 64% (kappa=0.1667, Table 3c) respectively. FDG PET-CT tended to give lower T and overall staging than MRI, as 8 of the 12 T4 tumors on MRI were reported as T2 or T3 on FDG PET-CT, and 8 of the 13 cases of stage IV disease on MRI were reported as stage II or III on FDG PET-CT. The difference mainly reflected that MRI detected more intracranial extension of NPC (Figures 1-4).

Table 4 summarizes data on metastatic LNs. MRI detected significantly more bilateral cervical LNs than FDG PET-CT, as these were found in all 14 patients on MRI but only 8

patients on FDG PET-CT ($p=0.03$). Similarly, MRI identified more bilateral retropharyngeal LNs than FDG PET-CT (9 vs. 6 patients). MRI detected supraclavicular lymphadenopathy in one patient that was not detected by FDG PET-CT. A level IV LN was revealed by FDG PET-CT but not by MRI (Figure 5).

There was no significant association between SUV_{max} and staging or size of the primary tumor. There was positive correlation between SUV_{max} and size of left cervical LNs measured on MRI (correlation coefficient=0.78, $p=0.006$). A similar positive correlation existed between SUV_{max} and size of left retropharyngeal LNs (correlation coefficient=0.81, $p=0.006$). We also found some correlation between SUV_{max} and EBV VCA IgG level at diagnosis (correlation coefficient=0.45), but this was not statistically significant (Figure 6). Since chemotherapy might reduce FDG uptake, we analyzed the data again after exclusion of 3 patients whose PET-CTs were done soon after initiation of chemotherapy. The results were similar with and without inclusion of these 3 patients, except that the correlation between SUV_{max} and size of left retropharyngeal LNs lost statistical significance (correlation coefficient=0.71, $p=0.09$). The correlation between SUV_{max} and size of left cervical LNs remained significant (correlation coefficient=0.83, $p=0.015$).

Follow-up PET-CT

Nine patients had 25 follow-up PET-CT scans. Twenty-four of these scans (8 patients) had MRI within 1 month for comparison. Tables 5a and 5b show the concordance between these scans. PET-CT and MRI were concordant in four-fifths of the scans. Concordance was 100% 9 months post-therapy. In those who achieved remission, PET-CT showed no disease 3-6 months earlier than MRI. There was no false positive or false negative PET-CT. In one patient with disease relapse who died of progressive disease, PET-CT showed lung and mediastinal metastases.

DISCUSSION

To the best of our knowledge, this is the first study evaluating FDG PET-CT in pediatric NPC patients. Previous studies of FDG PET-CT in adults were somewhat conflicting and might not be directly applicable to children.

We found the concordance between FDG PET-CT and MRI staging was not high. This is consistent with literature which showed concordance rates of 46-68% on T or overall staging [12, 13]. Some studies showed that MRI was superior to FDG PET and FDG PET-CT in assessing primary tumor extension [12, 13]. However, other studies have shown FDG PET-CT to be superior [5, 25, 26]. We found that the tumor usually appeared larger on MRI, possibly due to inclusion of inactive areas in measurements, leading to lower staging on FDG PET-CT. MRI may also be more sensitive for detection of subtle areas of tumor extension, for example, intracranial extension, that are too small for visualization by FDG PET-CT.

Consistent with previous studies [12, 15, 27], N staging showed better concordance between FDG PET-CT and MRI. FDG PET-CT is reported to have higher accuracy in detecting cervical LNs than conventional imaging [6, 15, 27, 28]. Xie [12] reported that FDG PET-CT was superior to MRI in revealing cervical but not retropharyngeal LNs. Tang [29] concurred that FDG PET-CT was less likely to detect retropharyngeal LNs. We found FDG PET-CT tended to underestimate both cervical and retropharyngeal LNs in children compared to MRI. On the other hand, MRI may overestimate nodal involvement based solely on size criteria. Since histology of lymph nodes is not routinely obtained, it is not possible to ascertain with certainty whether MRI overestimates neoplastic involvement compared to the true depiction of tumor involvement with FDG PET CT, or whether FDG PET CT

underestimates tumor involvement. Without histology which is considered the gold standard for diagnosis, the distinction between neoplastic and non-neoplastic lymphadenopathy is difficult to make, particularly in children, in whom enlarged lymph nodes are not uncommon.

Staging by conventional imaging is associated with prognosis of NPC [30, 31]. Although FDG PET-CT tended to yield a lower stage than MRI, this might not be inappropriate because subtle intracranial extension visible on MRI but not FDG PET-CT may not affect prognosis, and the relative under-staging by FDG PET-CT would not have altered treatment under the current protocol had FDG PET CT been utilized for staging. Correlation of FDG PET-CT staging with patient outcome is essential to ascertain the prognostic value of FDG PET-CT. However, this was not possible in the current study since the clinical outcome of patients studied from initial presentation was uniformly good.

We found that SUV_{max} of the primary tumor was higher than reported [32-35]. This may be related to a higher proportion of type III histology in children, as SUV_{max} in such tumors is higher [32, 35]. We also found that SUV_{max} positively correlated with size of LNs but not primary tumor. This might reflect difference in metabolic behavior between the primary tumor and metastatic LNs, as SUV_{max} in LNs was lower and had a wider variation. This could also reflect technical issues of activity recovery in small LNs compared with large primary tumors, as SUV of lymph node is subjective to partial volume effect and thus has a wide variation. Whether SUV_{max} is associated with tumor aggressiveness and prognosis in children is uncertain, as it was not associated with staging and we could not assess its effect on clinical outcome. Nevertheless, SUV_{max} might increase with T staging [32], and higher SUV_{max} has been correlated with poorer survival [33, 36]. Patients whose SUV_{max} of LNs higher than primary tumor also fared worse [36].

FDG PET-CT may help in detecting distant metastasis, as seen in our study and previous studies [5-7]. However, its sensitivity and specificity in detecting metastases are difficult to evaluate, as it was not compared with conventional imaging for different sites systematically. FDG PET-CT may replace bone scan as FDG PET might be more sensitive in detecting skeletal metastases [8].

FDG PET-CT may help in follow-up evaluation in pediatric NPC, as FDG PET-CT had fairly good concordance with MRI and had low false positive and false negative rates, consistent with adult studies [9-11, 34, 37, 38]. FDG PET-CT can screen the whole body in a single session and differentiate between active tumor and residual masses. FDG PET might have better sensitivity, specificity, and accuracy than MRI and result in management changes [37]. False positive results, however, may occur because of inflammation or osteoradionecrosis [39]. On the other hand, SUV_{max} 3 months after treatment may predict local relapse [34], and those who are downstaged by FDG PET after chemotherapy may have better survival [40]. We found that FDG PET-CT detected tumor clearance earlier than MRI, as MRI might give false positive signal due to scar. While we have found FDG PET-CT a useful tool in the diagnosis and follow-up of children with NPC, a prospective evaluation with uniform diagnostic imaging, treatment and monitoring would be required.

The radiation exposure from the FDG PET CT was quite low, approximately 10.2 mSv with our technique and equipment. This is of doubtful clinical concern in the context of the radiation exposure received as a result of therapy. On the other hand, PET-MRI may be better in evaluating lymph node metastases. Coronal MRI images would be the best for this purpose. However, currently our software only registers transverse sequences. Although they can be reformatted to coronal sections, the image quality would be degraded compared

to native coronal sequences. Therefore we did not pursue this option. The utility of PET-MRI certainly warrants evaluation in future studies.

Our study had several limitations. First, not all patients had baseline FDG PET-CT concurrent with MRI, and different patients had different imaging schedules, thus complicating the interpretation of results. Second, the sample size was small. However, it is already the largest study of FDG PET-CT in pediatric NPC. Third, there was lack of uniformity in the technical parameters for the MRI examinations. While this could affect the evaluation of tumor boundaries and measurements, it was not a significant factor in this investigation. Fourth, we did not have pathological verification of lymph nodes detected on MRI. Some of the nodes that were enlarged by size criteria on MRI might not have actually been metastatic. This is where PET may have been more accurate. Finally, the FDG PET-CT technique was devised for whole body screening, using CT parameters intended for attenuation correction and lesion localization without intravenous contrast. Modification of the technique and use of intravenous contrast enhanced CT for attenuation of emission FDG PET might possibly lower the discrepancies between PET-CT and MRI. On the other hand, it is possible that intravenous contrast may cause beam hardening artifacts if not optimally administered.

CONCLUSION

In pediatric NPC, FDG PET-CT tends to yield lower stage than MRI. It is also less sensitive in detecting bilateral cervical and retropharyngeal LN metastases based on size criteria of MRI. However, it is valuable in detecting distant metastasis and clarifying ambiguous findings on MRI. FDG PET-CT is also sensitive and specific for follow-up and enables earlier detection of disease clearance and simpler monitoring.

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REFERENCES

1. Ries, LAG.; Smith, MA.; Gurney, JG.; Linet, M.; Tamra, T.; Young, JL., et al., editors. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. National Cancer Institute, SEER Program; Bethesda, MD: 1999. NIH Pub. No. 99-4649;
2. Pappo, AS.; Rodiguez-Galindo, C.; Furman, WL. Management of infrequent cancers of childhood. In: Pizzo, PA.; Poplack, DG., editors. Principles and Practice of Pediatric Oncology. 6th ed. Lippincott Williams & Wilkins; Philadelphia: 2010. p. 1098-101.
3. Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: from biology to treatment. *Lancet Oncol.* 2003; 4:13–21. [PubMed: 12517535]
4. Stambuk HE, Patel SG, Mosier KM, Wolden SL, Holodny AI. Nasopharyngeal carcinoma: recognizing the radiographic features in children. *AJNR Am J Neuroradiol.* 2005; 26:1575–9. doi: 26/6/1575 [pii]. [PubMed: 15956532]
5. Lin XP, Zhao C, Chen MY, Fan W, Zhang X, Zhi SF, et al. Role of 18F-FDG PET/CT in diagnosis and staging of nasopharyngeal carcinoma. *Ai Zheng.* 2008; 27:974–8. doi:1000-467X200809974 [pii]. [PubMed: 18799039]
6. Chang JT, Chan SC, Yen TC, Liao CT, Lin CY, Lin KJ, et al. Nasopharyngeal carcinoma staging by (18)F-fluorodeoxyglucose positron emission tomography. *Int J Radiat Oncol Biol Phys.* 2005; 62:501–7. doi:S0360-3016(04)02713-0 [pii] 10.1016/j.ijrobp.2004.09.057. [PubMed: 15890593]
7. Yen TC, Chang JT, Ng SH, Chang YC, Chan SC, Lin KJ, et al. The value of 18F-FDG PET in the detection of stage M0 carcinoma of the nasopharynx. *J Nucl Med.* 2005; 46:405–10. doi:46/3/405 [pii]. [PubMed: 15750151]

8. Liu FY, Chang JT, Wang HM, Liao CT, Kang CJ, Ng SH, et al. [18F]fluorodeoxyglucose positron emission tomography is more sensitive than skeletal scintigraphy for detecting bone metastasis in endemic nasopharyngeal carcinoma at initial staging. *J Clin Oncol*. 2006; 24:599–604. doi:24/4/599 [pii] 10.1200/JCO.2005.03.8760. [PubMed: 16446332]
9. Yu DF, Zuo CT, Dai JZ, Dong MJ, Zhao J, Lin XT, et al. Application of 18F-FDG PET/CT scan in following-up of nasopharyngeal carcinoma after radiotherapy. *Ai Zheng*. 2004; 23:1538–41. doi: 1000467X200411s1538 [pii]. [PubMed: 15566675]
10. Wu DH, Chen LH. Clinical value of 18F-fluoro-2-deoxy-D-glucose positron emission tomography in detecting recurrent nasopharyngeal carcinoma at the parapharyngeal space after radiotherapy. *Di Yi Jun Yi Da Xue Xue Bao*. 2003; 23:159–61. [PubMed: 12581969]
11. Peng N, Yen S, Liu W, Tsay D, Liu R. Evaluation of the Effect of Radiation Therapy to Nasopharyngeal Carcinoma by Positron Emission Tomography with 2. *Clin Positron Imaging*. 2000; 3:51–6. doi:S109503970000039X [pii]. [PubMed: 10838400]
12. Ng SH, Chan SC, Yen TC, Chang JT, Liao CT, Ko SF, et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. *Eur J Nucl Med Mol Imaging*. 2009; 36:12–22. doi:10.1007/s00259-008-0918-7. [PubMed: 18704401]
13. King AD, Ma BB, Yau YY, Zee B, Leung SF, Wong JK, et al. The impact of 18F-FDG PET/CT on assessment of nasopharyngeal carcinoma at diagnosis. *Br J Radiol*. 2008; 81:291–8. doi: 81/964/291 [pii] 10.1259/bjr/73751469. [PubMed: 18344274]
14. Zhang GY, Liu LZ, Wei WH, Deng YM, Li YZ, Liu XW. Radiologic criteria of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma treated with radiation therapy. *Radiology*. 2010; 255:605–12. doi:255/2/605 [pii] 10.1148/radiol.10090289. [PubMed: 20413770]
15. Ng SH, Chang JT, Chan SC, Ko SF, Wang HM, Liao CT, et al. Nodal metastases of nasopharyngeal carcinoma: patterns of disease on MRI and FDG PET. *Eur J Nucl Med Mol Imaging*. 2004; 31:1073–80. doi:10.1007/s00259-004-1498-9. [PubMed: 15007565]
16. Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. *Radiology*. 2008; 249:203–11. doi:2491071753 [pii] 10.1148/radiol.2491071753. [PubMed: 18710963]
17. King AD, Ahuja AT, Leung SF, Lam WW, Teo P, Chan YL, et al. Neck node metastases from nasopharyngeal carcinoma: MR imaging of patterns of disease. *Head Neck*. 2000; 22:275–81. doi: 10.1002/(SICI)1097-0347(200005)22:3<275::AID-HED10>3.0.CO;2-N [pii]. [PubMed: 10748451]
18. Mao YP, Liang SB, Liu LZ, Chen Y, Sun Y, Tang LL, et al. The N staging system in nasopharyngeal carcinoma with radiation therapy oncology group guidelines for lymph node levels based on magnetic resonance imaging. *Clin Cancer Res*. 2008; 14:7497–503. doi: 14/22/7497 [pii] 10.1158/1078-0432.CCR-08-0271. [PubMed: 19010867]
19. Ng SH, Chan SC, Yen TC, Liao CT, Chang JT, Ko SF, et al. Comprehensive imaging of residual/recurrent nasopharyngeal carcinoma using whole-body MRI at 3 T compared with FDG-PET-CT. *Eur Radiol*. 2010; 20:2229–40. doi:10.1007/s00330-010-1784-9. [PubMed: 20393714]
20. Sakai O, Curtin HD, Romo LV, Som PM. Lymph node pathology. Benign proliferative, lymphoma, and metastatic disease. *Radiol Clin North Am*. 2000; 38:979–98. x. [PubMed: 11054964]
21. Ng WT, Lee AW, Kan WK, Chan J, Pang ES, Yau TK, et al. N-staging by magnetic resonance imaging for patients with nasopharyngeal carcinoma: pattern of nodal involvement by radiological levels. *Radiother Oncol*. 2007; 82:70–5. doi:S0167-8140(06)00601-3 [pii] 10.1016/j.radonc.2006.11.010. [PubMed: 17166610]
22. Edge SB, Byrd DR, Compton CC, Fritz AG. *AJCC Cancer Staging Manual*. 7th ed. Springer Verlag; Chicago, IL: 2009.
23. Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement*. 1960; 20:37–56.
24. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977; 33:159–74. [PubMed: 843571]

25. Gordin A, Golz A, Daitzchman M, Keidar Z, Bar-Shalom R, Kuten A, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in patients with carcinoma of the nasopharynx: diagnostic accuracy and impact on clinical management. *Int J Radiat Oncol Biol Phys.* 2007; 68:370–6. doi:S0360-3016(06)03642-X [pii] 10.1016/j.ijrobp.2006.12.028. [PubMed: 17324532]
26. Wang GH, Lau EW, Shakher R, Binns DS, Hogg A, Drummond E, et al. Clinical application of (18)F-FDG PET/CT to staging and treatment effectiveness monitoring of nasopharyngeal carcinoma. *Ai Zheng.* 2007; 26:638–42. doi:1000-467X200706638 [pii]. [PubMed: 17562272]
27. Zhang GY, Hu WH, Liu LZ, Wu HB, Gao YH, Li L, et al. Comparison between PET/CT and MRI in diagnosing lymph node metastasis and N staging of nasopharyngeal carcinoma. *Zhonghua Zhong Liu Za Zhi.* 2006; 28:381–4. [PubMed: 17045007]
28. Hu WH, Zhang GY, Liu LZ, Wu HB, Li L, Gao YH, et al. Comparison between PET-CT and MRI in diagnosing nodal metastasis of nasopharyngeal carcinoma. *Ai Zheng.* 2005; 24:855–60. doi:1000467X2005070855 [pii]. [PubMed: 16004815]
29. Tang LL, Ma J, Chen Y, Zong JF, Sun Y, Wang Y, et al. The values of MRI, CT, and PET-CT in detecting retropharyngeal lymph node metastasis of nasopharyngeal carcinoma. *Ai Zheng.* 2007; 26:737–41. doi:1000-467X200707737 [pii]. [PubMed: 17626750]
30. Cao KJ, Li Y, Xie GF, Hong MH. Prognostic factors in nasopharyngeal carcinoma in childhood and adolescence. *Zhonghua Zhong Liu Za Zhi.* 2006; 28:134–7. [PubMed: 16750020]
31. Sahraoui S, Acharki A, Benider A, Bouras N, Kahlain A. Nasopharyngeal carcinoma in children under 15 years of age: a retrospective review of 65 patients. *Ann Oncol.* 1999; 10:1499–502. [PubMed: 10643543]
32. Li J, Pan YD, Yin JL, Li XD. Analysis of standard uptake values of 18F-FDG PET/CT in relation to pathological classification and clinical staging of nasopharyngeal carcinoma. *Nan Fang Yi Ke Da Xue Xue Bao.* 2008; 28:1923–4. [PubMed: 18971200]
33. Lee SW, Nam SY, Im KC, Kim JS, Choi EK, Ahn SD, et al. Prediction of prognosis using standardized uptake value of 2-[(18)F] fluoro-2-deoxy-d-glucose positron emission tomography for nasopharyngeal carcinomas. *Radiother Oncol.* 2008; 87:211–6. doi:S0167-8140(08)00044-3 [pii] 10.1016/j.radonc.2008.01.009. [PubMed: 18237806]
34. Yen TC, Lin CY, Wang HM, Huang SF, Liao CT, Kang CJ, et al. 18F-FDG-PET for evaluation of the response to concurrent chemoradiation therapy with intensity-modulated radiation technique for Stage T4 nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006; 65:1307–14. doi:S0360-3016(06)00388-9 [pii] 10.1016/j.ijrobp.2006.02.031. [PubMed: 16863922]
35. Chang MC, Tsai SC, Lin WY. 18F-fluorodeoxyglucose uptake in different histological subtypes of nasopharyngeal carcinoma. *J Laryngol Otol.* 2009; 123:656–61. doi:S002221510800368X [pii] 10.1017/S002221510800368X. [PubMed: 18845034]
36. Xie P, Yue JB, Fu Z, Feng R, Yu JM. Prognostic value of 18F-FDG PET/CT before and after radiotherapy for locally advanced nasopharyngeal carcinoma. *Ann Oncol.* 2009 doi:mdp430 [pii] 10.1093/annonc/mdp430.
37. Chan SC, Yen TC, Ng SH, Lin CY, Wang HM, Liao CT, et al. Differential roles of 18F-FDG PET in patients with locoregional advanced nasopharyngeal carcinoma after primary curative therapy: response evaluation and impact on management. *J Nucl Med.* 2006; 47:1447–54. doi:47/9/1447 [pii]. [PubMed: 16954552]
38. Chen YR, Gu MX, Li WX, Pan Y. Detection of residue of nasopharyngeal carcinoma with FDG PET. *Ai Zheng.* 2002; 21:651–3. [PubMed: 12452068]
39. Zeng L, Huang XM, Lu TX, Zheng YQ, Chen QJ, Chen Y, et al. Diagnosis of recurrent or residual nasopharyngeal carcinomas in the skull base area with F-18-fluoro-deoxyglucose positron emission tomography. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2006; 41:517–20. [PubMed: 17007377]
40. Yen RF, Chen TH, Ting LL, Tzen KY, Pan MH, Hong RL. Early restaging whole-body (18)F-FDG PET during induction chemotherapy predicts clinical outcome in patients with locoregionally advanced nasopharyngeal carcinoma. *Eur J Nucl Med Mol Imaging.* 2005; 32:1152–9. doi:10.1007/s00259-005-1837-5. [PubMed: 15965687]

Fig. 1. Post-contrast axial T1-weighted MRI (A), axial PET (B) and corresponding unenhanced CT (C) and PET-CT fusion (D) images through the skull base of a 12-year-old patient with NPC demonstrate prominent involvement of tumor with the skull base and left masticator space (arrows)

Fig. 2.

Coronal STIR MRI (A), post-contrast coronal T1-weighted MRI (B) and corresponding coronal PET-CT fusion image (C) of the head and neck of the same patient as in Figure 1 reveal extension of a large NPC through the left foramen ovale and left foramen lacerum with involvement of the left cavernous sinus (arrows). MRI and PET-CT were both effective for detecting tumor extension through the skull base and into spaces adjacent to the nasopharynx

Fig. 3.

A post-contrast axial T1-weighted MRI image (A) through the skull base of a 15-year-old patient with NPC demonstrates subtle tumor extension into the left foramen lacerum (arrow) not appreciated on the corresponding axial PET (B), unenhanced CT (C) and PET-CT fusion (D) images

Fig. 4.

Coronal STIR (A) and post-contrast coronal T1-weighted MRI (B) images of the head and neck of the same patient as in Figure 3 again show subtle intracranial extension of a nasopharyngeal mass into the left foramen lacerum (arrows). This is not well visualized on corresponding PET-CT fusion image (C) (arrow)

Fig. 5.

An axial T2 weighted MRI image of the neck (A) of a 15-year-old patient with NPC demonstrates two adjacent level IV lymph nodes in the left side of the neck that do not meet the size criteria for pathologic nodes, although the asymmetry and grouping of these nodes in the setting of NPC may raise some concern for metastases. A PET image obtained at the same level (B) demonstrates intense radiotracer uptake in the more lateral of the two nodes allowing much more confident diagnosis of metastatic disease

Fig. 6.
Correlation between SUV_{max} and EBV VCA IgG level at diagnosis

Table 1

Characteristics of patients (N=18)

Characteristics	Number
Sex	
Male	16
Female	2
Race	
White	6
African-American	11
American Indian	1
Age at diagnosis (years)	
Median	13.6
Range	8.4-17.9
Histopathology	
Type I or II	3
Type III	10
Unspecified	5
EBV serology (signal to cutoff ratio) – median (range)	
Anti-VCA IgG	4.73 (1.19-6.27)
Anti-VCA IgM	0.34 (0.11-1.18)
EBNA antibody	4.58 (3.73-5.79)

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Table 2

Size of NPC and staging at presentation for patients with baseline PET-CT

Patient number	MRI Size (cm)	PET SUV	MRI T Stage	PET T Stage	MRI N Stage	PET N Stage	MRI Stage	PET Stage
1	5.9	NA ^a	T4	T3	N2	N2	IVA	III
2	5.1	NA	T4	T4	N2	N2	IVA	IVA
3	3.7	8.8	T4	T2	N2	N1	IVA	II
4	3.0	15.4	T4	T2	N2	N1	IVA	II
5	3.9	12.2	T3	T2	N2	N2	III	III
6	4.6	13.7	T4	T3	N2	N2	IVA	III
7	4.7	8.3	T4	T2	N2	N1	IVA	II
8	4.9	32.0	T4	T2	N2	N2	IVA	III
9	4.2	24.9	T4	T3	N2	N2	IVA	III
10	3.3	19.6	T1	T2	N3b	N3b	IVB	IVB
11	4.1	24.8	T4	T3	N2	N2	IVA	III
12	4.8	15.7	T4	T4	N2	N3b	IVA	IVB
13	5.7	12.7	T4	T4	N3b	N2	IVB	IVA
14	5.5	14.9	T4	T4	N2	N2	IVA	IVA
Mean	4.5	16.9						

^aNA: not available due to technical issue

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Table 3a
Concordance between staging by FDG PET-CT and MRI at presentation [Kappa=0.104 (95%CI: -0.090, 0.298)]

Staging by FDG PET-CT		II	III	IV	Total
Staging by MRI	II	0	0	0	0
	III	0	1	0	1
	IV	3	5	5	13
	Total	3	6	5	14

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Table 3b
Concordance between T staging by FDG PET-CT and MRI [Kappa=0.0870 (95%CI: -0.0898, 0.2637)]

Staging by FDG PET-CT					
	T2	T3	T4	Total	
Staging by MRI	T1	1	0	0	1
	T3	1	0	0	1
	T4	4	4	4	12
	Total	6	4	4	14

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Table 3c
Concordance between N staging by FDG PET-CT and MRI [Kappa=0.1667 (95%CI: -0.2622, 0.5955)]

Staging by FDG PET-CT				
	N1	N2	N3b	Total
N1	0	0	0	0
N2	3	8	1	12
N3b	0	1	1	2
Total	3	8	3	14

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Table 4

Size of regional LNs by FDG PET-CT and MRI

Patient Number	Left cervical		Right cervical		Left retropharyngeal		Right retropharyngeal	
	MRI Size (cm)	SUV _{max}	MRI Size (cm)	SUV _{max}	MRI Size (cm)	SUV _{max}	MRI Size (cm)	SUV _{max}
1	1.5	NA	2.4		1.6		1.8	NA
2	4.2	NA	1.0 ^a		1.9		2.6	NA
3	2.0	8.0	1.1		1.4	8.0		
4	2.3	17.1	1.2		1.7	12.4		
5	2.8	12.2	1.2	5.3	0.9	11.9		
6	1.3	6.3	0.8 ^a	2.9	1.5	6.5	0.9	3.3
7	2.6	10.3	1.1		0.9	6.0	1.2	6.5
8	2.2	30.8	1.0 ^a	6.6				
9	1.8	7.8	1.0 ^a	3.9	2.6	22.8	0.9	20.8
10	2.1	18.5	3.5	25.1	1.4	20.0	2.2	15.7
11	2.2	18.3	1.0 ^a		1.5	13.5	1.2	
12	1.8		2.7	7.8	1.1		0.8	
13	2.2	9.0	0.9 ^a	5.9	1.1	5.0	1.0	5.4
14	1.5	2.7	1.2		1.1	3.9		
Median	2.2	10.3	1.1	5.9	1.4	10.0	1.2	6.5
Mean	2.2	12.8	1.4	8.2	1.4	11.0	1.4	10.3

^aThese jugulodigastric nodes under 1.1cm were part of a cluster of nodes.

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Table 5a

Concordance of follow-up FDG PET-CT and MRI in different patients

Patient no.	Number of scans	Disease found on both imagings	Disease found on MRI but not FDG PET-CT	No disease found on both imagings	Concordance
4	5	1	2	2	60%
5	8	0	3	5	62.5%
6	5	0	0	5	100%
11	1	1	0	0	100%
14	1	0	1	0	0%
15	1	0	0	1	100%
16	1	0	0	1	100%
17	2	0	1	1	50%
TOTAL	24	2	5	17	79.2%

Table 5b

Concordance of follow-up FDG PET-CT and MRI at different times

Timing of scans	Number of patients	Disease found on both PET-CT and MRI	Disease found on PET-CT but not on MRI	No disease found on both PET-CT and MRI	Concordance
After 3 courses of chemotherapy	4	1	2	1	50%
End of therapy	4	0	1	3	75%
3-5 months post-therapy	4	1	1	2	75%
9-12 months post-therapy	4	0	0	4	100%
15-18 months post-therapy	3	0	0	3	100%